SUPPORT FOR THE AMENDMENTS

Applicants have added new Claims 56-60. Support for the composition not being coated with an enteric coating can be found in the examples, particularly Examples 14 and 20.

No new matter has been added. Claims 8-48, and 54-60 are pending in the present application.

REMARKS/ARGUMENTS

Present Claims 8-11 relate to effervescent pharmaceutical compositions comprising levodopa methyl ester and an acid-base couple, wherein administering a single oral dose of said composition to a human provides to said human a maximum plasma concentration of levodopa at about 0.3 hours (T_{max}) after said administering.

Present Claims 12-16 and 54 relate to pharmaceutical compositions comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides to said human a mean maximum plasma concentration of levodopa (C_{max}/dose) of about 9.6 ng/mL/[mg LDME] after said administering.

Present Claims 17-21 and 55 relate to pharmaceutical compositions comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides to said human an area under the curve of levodopa in plasma from 0 to 1 hour (AUC_{1h}/dose) of about 5.3 ng·hr/mL/[mg LDME] after said administering.

Present Claims 22-25 relate to pharmaceutical compositions comprising levodopa methyl ester and an acid-base couple, wherein administering a single oral dose of said

composition to a human provides to said human a ratio of about 2.7 of mean plasma concentration of levodopa at 15 minutes after said administering compared to 60 minutes after said administering.

Present Claims 26-34 relate to pharmaceutical compositions comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides to said human a mean plasma concentration (C_p) of levodopa of about 8.8 ng/mL/[mg LDME] 15 minutes after said administering.

Thus, the present claims are drawn to pharmaceutical compositions comprising levodopa methyl ester (LDME) and an acid-base couple, wherein administering a single oral dose of said composition to a human provides:

- a maximum plasma concentration of levodopa at about 0.3 hours (T_{max}) after said administering (claim 8);
- a mean maximum plasma concentration of levodopa (C_{max}/dose) of about 9.6 ng/mL/[mg LDME] after said administering (claim 12);
- an area under the curve of levodopa in plasma from 0 to 1 hour (AUC_{1h}/dose) of about 5.3 ng·hr/mL/[mg LDME] after said administering (claim 17);
- a ratio of about 2.7 of mean plasma concentration of levodopa at 15 minutes after said administering compared to 60 minutes after said administering(claim 22);
- a mean plasma concentration (C_p) of levodopa of about 8.8 ng/mL/[mg LDME] 15 minutes after said administering (claim 26).

and wherein:

- said acid-base couple is sodium glycine carbonate -fumaric acid (claims 9, 13, 19, 23, and 32);

- said composition further comprises carbidopa monohydrate (claims 10, 14, 20, 24, and 33); and
- the weight ratio of levodopa methyl ester to carbidopa monohydrate to sodium glycine carbonate to fumaric acid is about 1.0:0.09:1.7:1.1, respectively (claims 11, 15, 21, 25, and 34).

In particular the composition of the present invention:

- because of its light effervescence and rapid disintegration is a *fast dissolving* formulation
- after single oral dose administration show a more *rapid absorption* and an active ingredient higher exposure during the *first hours after administration* in comparison to the standard commercial formulation (see paragraph [0116]).

In fact all the pharmacokinetics parameters detailed in the independent claims relate to the fast oral absorption profile of levodopa and carbidopa released from effervescent tablets according to the present invention.

The rejection of Claims 8, 12, 17, 18, 22, and 26-31 under 35 U.S.C. § 103(a) in view of U.S. Patent No. 3,961,041 (Nishimura et al.) is respectfully traversed. Nishimura et al. describe effervescent, ***enteric coated*** formulations containing L-DOPA. The goal of Nishimura et al. is to deliver a higher blood-concentration of L-DOPA without the need of massive dosing dosing which may result in side effects:

> L-DOPA is the drug of choice in the treatment of Parkinson's Disease. It is reported, however, that this drug is only therapeutically effective when it is orally administered in massive doses, such as 2 to 3 grams per day or even as much as 8 grams per day, depending upon the seriousness of the disease. It is also known that therapeutic results can be obtained by administering 50 to 100 mg per day of the drug via intravenous injections. On the other hand, L-DOPA causes marked side effects when such massive dosing is administered. As such, some patients cannot realize

> thereapeusis because the side effects of L-DOPA eliminate therapeutic responses from the patient.

See, Col. 1, lines 16-28.

> It is obvious, based on the foregoing, that a great need exists for an orally administrable L-DOPA formulation which will permit L-DOPA or any derivative thereof capable of reverting to L-DOPA in vivo to achieve a substantial therapeutic effect without initiating accompanying side effects.

See, col. 2, lines 14-19.

Nishimura et al. also discloses that L-DOPA is unstable in the gastrointestinal tract, especially in the stomach and that the decomposition of L-DOPA in the stomach is remarkable (*see*, col. 1, lines 35-42).

Accordingly, the solution proposed by Nishimura et al. is a standard ***enteric coated*** dosage form designed to result in the L-DOPA being absorbed in the small intestine:

> Considering the above, the present inventors have developed an enteric coated L-DOPA formulation which is characterized as (1) not decomposed in the stomach, (2) not subject to decarboxylation in the intestine, and (3) highly absorbed through the gastrointestinal tract. Essentially, the present invention concerns delivering L-DOPA or any derivative thereof capable of enzymatically cleaving and reverting to L-DOPA in vivo via an effervescent-***enteric coated*** tablet. By using such a formulation, the effervescent nature thereof permits total disintegration and release of L-DOPA all at once, ***when L-DOPA or any suitable derivative thereof,*** as characterized above, ***reaches the intestine***. That is, the effervescent-***enteric coated preparation permits L-DOPA to enter the small intestine without undergoing decomposition in the stomach after oral administration***.

See, col. 2, lines 22-38.

Thus, a key feature of the formulation of Nishimura et al. is the ***enteric coating*** which inhibits decomposition of the L-DOPA in the stomach. However, a result of the presence of the enteric coating in the formulations of Nishimura et al. is that the formulations of this reference do not exhibit the pharmacokinetic properties required by the present claims.

In support of the assertion that the formulations according to Nishimura et al. do not exhibit the pharmacokinetic properties required by the present claims, Applicants direct the

Examiner's attention to the results presented in Figure 1 of this reference. As the Examiner will note all of the formulations tested in Nishimura et al. exhibit a maximum blood concentration of L-DOPA at a time beyond 1 hour.

In sharp contrast, present Claim 8 recites a maximum plasma concentration of levodopa at about 0.3 hours. Thus, the presently claimed formulation result in a very rapid release and consequent rapid absorption of levodopa methyl ester.

There is nothing in Nishimura et al. which would even remotely suggest preparing a formulation which exhibits such a short maximum concentration time. To the contrary, Nishimura et al. specifically designs the formulation to avoid decomposition in the stomach, i.e. to result in a longer time until maximum concentration.

For these reasons, the present claims are not obvious in view of Nishimura et al. Accordingly, the rejection should be withdrawn.

The rejection of Claims 8-34, 54, and 55 under 35 U.S.C. §103(a) in view of U.S. Patent No. 4,826,875 (Chiesi) in view of U.S. Patent No. 5,211,957 (Hagemann et al.) or U.S. Patent No. 5,503,846 (Wehling et al.) is respectfully traversed. Applicants respectfully submit that the combined disclosures of Chiesi, Hagemann et al., and Wehling et al. fail to disclose, explicitly or implicitly, or suggest all the limitations of the claims and, thus, fail to render the claimed invention obvious.

Chiesi discloses that levodopa methyl ester can be used as active principle of pharmaceutical compositions. In particular, Chiesi describes pharmaceutical compositions for oral or sublingual administration in solid (*i.e.* tablets) or liquid form. However, the compositions of Chiesi do not contain an effervescent couple.

Hagemann et al. discloses effervescent tablets and provided a long list of components (see, col. 5, lines 5-13 and 20-23). Similarly, Wehling et al. effervescent formulations and

also discloses a long list of components acid and base components (see, col. 7, lines 17-25 and 5-16). Thus, Hagemann et al. and Wehling et al. both only disclose glycine sodium carbonate (GSC) as one possibility among a long list of bases and fumaric acid or maleic acid as one possibility among a long list of acids. Neither of these references actually describe the combination of these specific components.

In fact, no examples are given by Hagemann et al. or Wehling et al. of the use of the specific effervescent couples GSC+ fumaric acid or GSC+ maleic acid and no advantages by the use of these couples with respect to other possible couples are reported. To the contrary, Hagemann et al. cites citric acid as the preferred acid and sodium bicarbonate as the preferred source of carbon dioxide, while Wehling et al. cites crystallized citric acid as the preferred acid and potassium or sodium carbonate as the preferred base.

Thus, there is nothing in either Hagemann et al. or Wehling et al. which would lead to the actual combination GSC+ fumaric acid or GSC+ maleic acid.

In any event, the inventors have found that the presently claimed compositions exhibit a number of advantages which could not have been expected based on the teachings of Chiesi, Hagemann et al., and Wehling et al.

Specifically, the presently claimed compositions exhibit improved pharmacokinetic properties as even compared to the ***solution*** formulation disclosed in Chiesi. In this regard, the Examiner's attention is directed toward the pharmacokinetics data presented in the following table.

	Claimed invention	Chiesi (calculated)
T_{max} (claim 8)	About 0.3 h	0.75h
C_{max}/dose (claim 12)	About 9.6 ng/mL/[mg LDME]	6.0 ng/mL/[mg LDME]
AUC_{1h}/dose (claim 17)	about 5.3 ng·hr/mL/[mg LDME]	4.3 ng·hr/mL/[mg LDME]
ratio of mean plasma concentration of levodopa at 15 minutes after administration compared to 60 minutes after said administration (claim 22)	About 2.7	0.83
mean plasma concentration of levodopa (C_p) 15 minutes after said administration (claim 26)	About 8.8 ng/mL/[mg LDME]	3.5 ng/mL /[mg LDME]

In the table, the various parameters have the following meanings:

- T_{max} (i.e., time to maximum concentration)
- C_{max}/dose (i.e., mean maximum plasma concentration /dose [mg LDME])
- AUC_{1h}/dose (i.e., area under the curve of levodopa in plasma from 0 to 1 hour/dose [mg LDME])
- ratio of mean plasma concentration of levodopa at 15 minutes after administration compared to 60 minutes after said administration,
- mean plasma concentration of levodopa (C_p) 15 minutes after said administration.

Thus, the claimed formulations provide superior pharmacokinetics as compared to the formulation of Chiesi. For example, the formulation of Chiesi results in a maximum concentration peak at ***40-45 minutes*** from administration (*see*, col. 5, lines 30-32). Further, in Table I, Chiesi show that the maximum plasmatic levels of levodopa are obtained at about 45-80 minutes (i.e., 0.75-1.3 hr) after the administration of LDME. In sharp contrast, with

the presently claimed formulations, the maximum plasma concentration of levodopa is achieved in about 0.3 hours (Tmax: see Table 7), corresponding to about ***18-20 minutes***. Accordingly, the effervescent composition of the present invention provides for a shorter time to levodopa maximum concentration as compared to the composition of Chiesi.

It should be noted that the values of the pharmacokinetic parameters for the formulation of Chiesi are derived from the results presented in Table 1 on col. 5 of this reference and are the result of administration of the formulation of Example 1, which is a ***solution*** formulation.

There is no suggestion in any of the cited references that it would be possible to prepare an effervescent formulation which would actually result in a faster absorption than the ***solution*** formulation of Chiesi. Accordingly, the results presented above, could not have been expected from the cited references and ensure the patentability of the present claims.

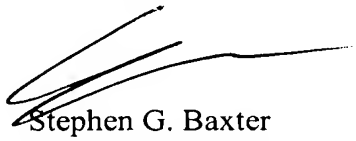
For all of these reasons, the rejection should be withdrawn.

Finally, with respect to the withdrawn method claims, the Examiner is reminded of rejoinder as discussed in MPEP §821.04. Applicants note that should the examined product claims (i.e., Claims 8-34) be found allowable, withdrawn process claims (minimally Claims 35-48) should be rejoined and examined as these claims contain all the limitations of the examined product claims. An action to this effect is requested.

Applicants submit that the present application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)